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Unveiling the biocatalytic aromatizing activity of monoamine oxidases MAO-N and 6-HDNO: development of chemoenzymatic cascades for the synthesis of pyrroles.

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ABSTRACT: A chemoenzymatic cascade process for the sustainable production of pyrroles has been developed. Pyrroles were synthesised exploiting the previously unexplored aromatizing activity of monoamine oxidase enzymes (MAO-N and 6-HDNO). MAO-N/6-HDNO whole cell biocatalysts are able to convert 3-pyrrolines into pyrroles under mild conditions and high yields. Moreover, MAO-N can work in combination with ruthenium Grubbs' catalyst leading to the synthesis of pyrroles from diallyl-amines/anilines in a one-pot cascade metathesis-aromatization sequence.

KEYWORDS: MAO-N, biocatalysis, chemoenzymatic cascade, metathesis, pyrrole

INTRODUCTION

The occurrence of aromatic nitrogen heterocycles in many natural and synthetic biologically active compounds represents an incentive toward the development of new synthetic methodologies toward these important chemicals.[1] It is estimated that more of 50% of the bestselling drugs contain a nitrogen heterocyclic nucleus, thus fueling a demand for broadly applicable synthetic methods that deliver aromatic heterocycles in high yield. We recently discovered a new class of pyrroles endowed with potent activity against drug-resistant tuberculosis and thus we became interested in finding new sustainable approaches for the production of this class of compounds.[2] Typical approaches for the synthesis of pyrroles include the Paal−Knorr and Clauson−Kass reactions,[3] the aza-Wittig reaction[4] or other multicomponent approaches.[5] Approaches to pyrroles under relatively mild conditions via iron or palladium catalysed Paal-Knorr reactions on water have been also described.[6] However, the structural features of the reagents required in the latter methods or the side products formed may represent

a limitation in the scope of these reactions. Recently, olefin ring-closing metathesis (RCM) emerged as a powerful and effective reaction for the two steps synthesis of many functionalized pyrroles from acyclic precursors. Donohoe[7] and Rutjies[8] first developed a two steps sequence to pyrroles from diallylamines **1** via ring-closing metathesis (RCM) followed by aromatization mediated by $RuCl_3$, Pd/C, $FeCl_3$ or ^tBuOOH (Figure 1). This latter step is supposed to occur through the oxidation of the amine **2** into the corresponding iminium intermediate **3** leading in turn to pyrrole **4** by tautomerization. The direct oxidation of amines into imines or iminium ions still represents a challenge in organic synthesis and only few approaches have been described so far. These methods rely on the use of metal catalysts such Fe, Pd, Ru in the presence of oxygen or TEMPO and often require harsh reaction conditions.[9] However, in Nature, the conversion of an amine group into the corresponding imine is a common biochemical transformation that is catalysed by monoamine oxidase (MAO) enzymes.[10] MAO enzymes catalyse the oxygen-dependent oxidation of amines into imines which are in turn hydrolysed into aldehydes under aqueous conditions. Due to their unique properties, the monoamine oxidase variants from *Aspergillus niger* (MAO-N) have found a broad application also as biocatalysts for stereocontrolled syntheses[11] and have been extensively used in a variety of synthetic transformations. In particular, MAO-N have been widely studied as biocatalysts for the production of enantiomerically pure amines through the selective oxidation and deracemization of a range of chiral aliphatic substrates.[11] Herein, we describe a new sustainable approach for the synthesis of pyrroles unveiling for the first time the ability and versatility of MAO-N enzymes in catalysing the oxidation-aromatization of 3-pyrrolines **2** into pyrroles **4**. In addition, a one-pot chemoenzymatic cascade reaction for the synthesis of pyrroles through the *in-situ* combination of RCM reactions with the MAO-N aromatizing biocatalysts is described.

RESULTS AND DISCUSSION

The MAO-N aromatization of 3-pyrrolines substrates **7** and **10**, synthesised via RCM as reported in Scheme 1,[12] was first investigated. Freeze-dried whole cells containing MAO-N variants D5, D9 and D11 were selected on the basis on their known activity and selectivity toward structurally related pyrrolidines.[11] In addition, the oxidizing/aromatizing properties of the recently developed nicotine oxidase biocatalyst 6-HDNO E350L/E352D[13] were also explored. All the enzymatic biotransformations were initially carried out at 37 ºC in a buffer solution (pH = 7.8) using DMF as co-solvent where appropriate, according to standard protocols.[11a] The data are summarised in Table 1 and Table 2. The aryl-pyrrolines **7** were converted into pyrroles **11** with moderate to excellent yields depending on the substituent on the aryl group. The phenyl-pyrroline **7a** was converted into pyrrole **11a** by MAO-D5 and 6-HDNO in good amount (61%), whilst the variant D9 led to **11a** in only 32% conversion. Full conversion (>99%) of pyrrolines **7d** and the 2-methyl-substituted **7i** was observed with MAO-D5, whilst D9 and 6-HDNO proved to be less active. On the other hand, no conversion of the pyrrolines **7j-k** into pyrroles bearing a phenyl substituent at C2 and C3 respectively was observed. Steric factors prevented **7j-k** to enter into the catalytic site of MAO-D5 as shown by docking simulation in Figure 2.[14]Docking simulations were carried out in order to show the interaction of pyrrolines **7a** and **7k** within the catalytic site of MAO-D5 and explain the experimental data. Whilst **7a** fits within the catalytic site of MAO-D5, the phenyl substituent (in yellow) of the bulkier **7k** lays in a region of the catalytic site where an amino acid residue is located, thus preventing **7k** from entering the enzyme's active site and being aromatized. Again, no conversion was observed when **7j-k** were treated with the variant MAO-D11.The substrates **7g** and **7h** bearing an electron withdrawing substituent on the aromatic ring (-NO_2 and -CN respectively) were not converted into

corresponding pyrroles. Despite the exact mechanism of action of MAO has not fully elucidated,[15] one of the proposed model suggests that the oxidation of amines proceeds through a nucleophilic mechanism where the amine attacks the FAD by nucleophilic addition and it is in turn oxidised to imine leading to the formation of the reduced FADH2.[16] Thus, it is likely that the electron withdrawing substituents on the phenyl ring of **7g-h** reduce the electronic density and consequently the nucleophilicity of the pyrroline nitrogen, thus preventing the attack of **7g-h** to FAD and their following oxidation into pyrroles.[17] As further confirmation of this assumption, the more nucleophilic alkyl pyrrolines **10a-f** were fully converted (>99%) by MAO-D5. Table 2. Lower conversion (51-61%) values were observed when the same biotransformations were carried out with MAO-D9. The nicotine oxidase 6-HDNO was able to fully oxidise the benzyl-pyrroline **10a** (95%) while lower conversion (65%) was observed for the bulkier cyclohexyl derivative **10f**. Pyrroline **10g** bearing a bulky substituent on the nitrogen was oxidised in low yields as well as the benzyl pyrrolines **10h-i** bearing two methyl substituents on the heterocyclic nucleus (48-51% of **12h-12i**). Finally, the aromatization of **10j-k** bearing a phenyl substituent on the pyrroline nucleus was investigated. Interestingly, the secondary pyrroline **9c** was poorly converted into the pyrrole **12l** by all the set of amino oxidase catalysts, whilst excellent conversion values were observed for the tertiary pyrroline **10j**. Lower conversion for **10k** was observed due to steric factors.

One of the most intriguing challenge for chemists and biologists is represented by the possibility to combine chemo- and enzymatic catalysis in a concurrent fashion, due to the compatibility issues of the catalysts and the different reaction conditions in which these generally operate.[18] The combination of chemo- and bio-catalysis offers opportunities to outperform sequential transformations and the development of one-pot multistep-cascade reactions

containing both transition-metal catalysts and enzymes is highly appealing in terms of both selectivity and synthetic efficiency. Moreover, cascade reactions offer additional benefits other than the immediate succession of the individual transformations, such as the almost instantaneous consumption of toxic or unstable intermediates without the requirement of intermediate isolation or functional group protection strategies, leading to safer processes and to the reduction of undesired side products. Thus, the combination of RCM reactions with MAO biocatalysts in the same reaction medium was investigated with the aim to develop a chemoenzymatic cascade synthesis of pyrroles from allyl-amines/anilines as shown in Table 3. The diallylaniline **6a** was first dissolved in a 1:60 DMF/Buffer pH=7.8 solution and treated simultaneously with 5mol% Grubbs' catalyst **GII** and MAO-D5 at 37 ^{o}C. Aniline **6a** was recovered from the reaction mixture after 24h and only 10% of 3-pyrroline **7a** was obtained, whilst no traces of the pyrrole **11a** were detected (*entry 1*). On the opposite, 90% of **7a** was obtained when the same biotransformation was performed in 1:60 acetone/buffer mixture. Again no traces of **11a** were observed (*entry 2*). It is known that acetone is a more suitable solvent for RCM reaction than DMF, thus accounting for the higher amount of **7a** detected in the second case.[19] Increasing the co-solvent/buffer ratio to 1:4 and using different water-miscible co-solvents (THF and DMSO) (*entries 4-7*) did not affect the outcome of the biotransformation. In all cases, variable amounts of the RCM product **7a** were detected but no traces of the desired pyrrole **11a** were obtained. Previous works demonstrated that MAO biocatalysts suffer the co-presence of chemocatalysts in the same reaction medium.[11c] Recently, Hartwig and Zhao showed that iso-octane can work as excellent co-solvent in chemoenzymatic biotransformations, due to its ability to form a biphasic system with low mass transfer together with the buffer solution.[20,18a] When the chemoenzymatic reaction was carried out in an iso-octane/buffer 1:4 mixture (entry 8),

the pyrrole **11a** was obtained as main product in high yield together with negligible amount of **7a**. The use of the non-water miscible co-solvent iso-octane proved to be crucial to prevent the interaction between the Ru-catalyst and the MAO-D5 and avoid the deactivation of the enzyme probably due to the Ru binding. In fact, in an immiscible iso-octane-buffer mixture, the homogeneous Ru-catalyst is partioned in the organic phase, while the biocatalyst is suspended in water. The diene **6a** is converted by **GII** into the 3-pyrroline **7a** in the iso-octane phase, and then**7a** is oxidized by MAO-D5 leading to the desired pyrrole **11a**. The biphasic reaction medium acts mimicking the compartmentalization of cellular processes allowing thus the cascade reactions to take place in an efficient manner. The scope of the chemoenzymatic cascade was then investigated as shown in Table 4. Pyrrole **11a** was obtained in 88% conversion and 78% isolated yield (method A). With the aim to improve the yield of the reaction, a two steps method was also set up. Allylaniline **6a** was mixed with **GII** and MAO-D5 and stirred at 37 ^{o}C for 6 h, after which time an additional amount of MAO-D5 was added (method B). Higher conversion (95%) was observed with the one-pot two steps protocol, but **11a** was isolated in lower yield (65%) (*entry 2*). It is noteworthy that the treatment of **7a** with MAO-D5 led to **11a** with 61% conversion, whilst the chemoenzymatic cascade led to **11a** from **6a** in 95% conversion.It is plausible that in the chemoenzymatic cascade the aniline **6a** is converted into the pyrroline **7a** slowly. As soon as **7a** if formed, it is immediately oxidised by MAO-D5 affording **11a**. In this way only a low amount of **7a** is oxidised by MAO-D5 time by time allowing a more rapid enzyme turnover. Similarly, pyrroles **11b** and **11l** (*entries 5-6, 11-12*) were isolated in high yields when the one-pot one-step method A was used whilst higher conversion values were observed with the two steps one-pot protocol B. As general trend, excellent conversion and high yields were observed for pyrroles bearing chloro- (**11l**), methyl-(**11m**) and alkoxy-substituents

(**11n**, **11o**) (*entries 11-17*). Medium to good conversion (50-75%) was observed for pyrroles **11d-e** (*entries 6-8*) probably due to the lower reactivity of electron-rich diallylanilines toward the RCM reaction. In fact, several factors must be taken into account in the chemoenzymatic cascade, such as the reactivity of anilines in the metathesis reaction, where electron donating substituents on the phenyl ring disfavour the ring closure, as well as the biocatalytic oxidation, where electron withdrawing substituents prevent the pyrroline oxidation.

The chemoenzymatic cascade of alkyl-diallylamines was finally investigated. Not surprisingly, the benzylpyrrole **12a** was obtained in low yield (*entry 18*) due to the poor reactivity of alkyl-diallylamines toward RCM reactions.[21] It is well documented that tertiary amines inactivate **GII** forming stable complexes and thus preventing the RCM cyclization. On the other hand, the inactivation of **GII** by amines can be overcome if branched diallylamines are used as substrates. In fact, branched pyrroles **12e** and **12g** were obtained from the corresponding allylamines in good yields (*entries 19-20*).

The attempt to obtain the pyrrole **12l** via the chemoenzymatic cascade from the corresponding secondary amine was also unsuccessful (*entry 21*). An alternative route was thus developed (Scheme 2) leading to **12l** in one-pot from the chloroethyl-carbamate **8**. The carbamate protecting group allows the RCM reaction of **8** to take place almost instantaneously (around 20 min) leading to the intermediate **13**. The chloroethyl-carbamate protecting group is labile under the reaction conditions and it is slowly cleaved leading to pyrroline **9c**. The latter is in turn oxidised by MAO-D5 affording the desired pyrrole **12l** in 42% overall yield. Finally, the present methodology has been applied to the synthesis of a series of pyrrole analogues of the antitubercular agents recently described by us.[2] As an example, the pyrroline **7b** was converted in a single step into the pyrrole **14** by treatment with MAO-D5 followed by in situ Mannich

reaction with phenylpiperazine and formaldehyde. (Scheme 3). In addition, the pyrrole **12m**,[22] precursor of the natural alkaloid myrmicarin217, was synthesised from the diene **6t** via the chemoenzymatic method A in 20% isolated yield.[23] (Scheme 3).

CONCLUSIONS

In conclusion, the aromatizing properties of MAO-N biocatalysts have been disclosed for the first time. MAO-N, and in particular the variant D5, catalyse the aromatization of a wide range of *N*-aryl- and *N*-alkyl-3-pyrrolines into the corresponding pyrroles. The ability of MAO-N biocatalysts to work in a concurrent way together with Grubbs' catalyst has been also investigated leading to the development of a chemoenzymatic cascade reaction for the one pot synthesis of pyrroles from dilallyl-anilines and diallyl-amines. This work represents the first example of a chemoenzymatic cascade combining in the same reaction medium MAO-N with a metal-catalyst, other than boron reducing agents. The new methodology represents a robust and sustainable alternative to standard catalytic methods for the synthesis of pyrroles, which generally require the use of group specific or poorly available reagents, higher temperatures to promote the aromatization step and lead to the formation of several side products. Finally, the chemoenzymatic methodology is currently used in our laboratory for the synthesis of novel antitubercular pyrrole derivatives.

FIGURES

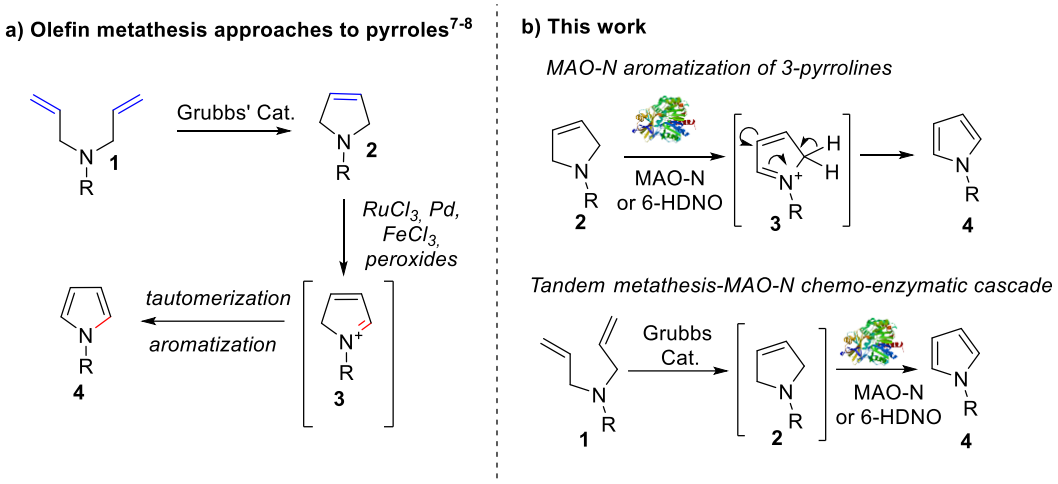


Figure 1. Classical RCM approaches for the synthesis of pyrroles and MAO-N aromatization of 3-pyrrolines.

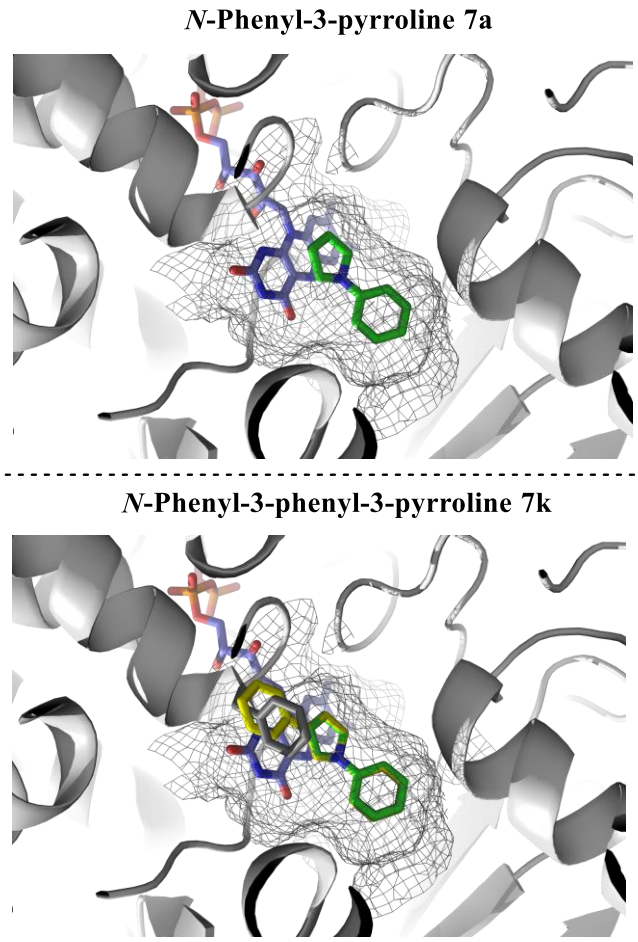
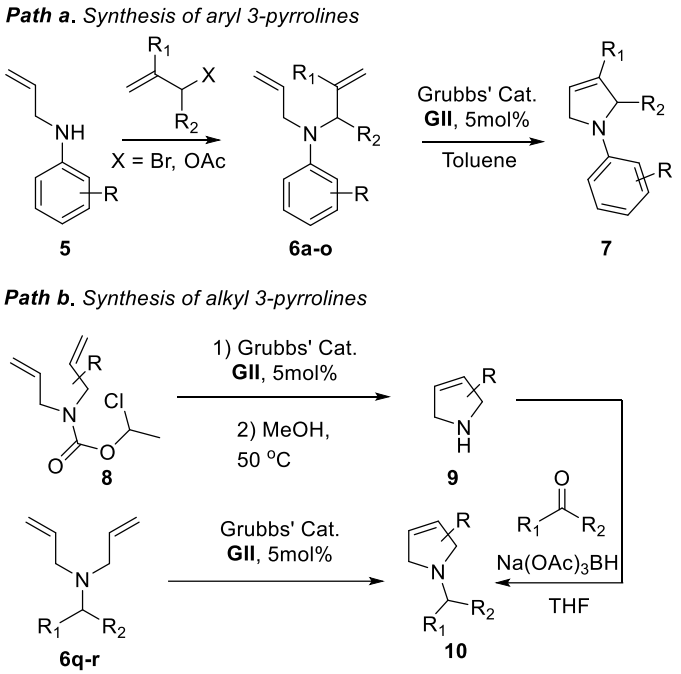
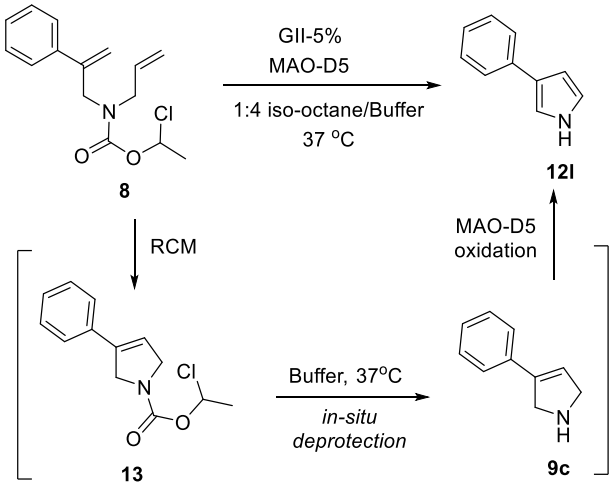


Figure 2. Docking of pyrroline **7a** into the MAO-D5 catalytic site and superposition of **7k** on the predicted conformation of **7a**. The additional phenyl ring at C3 (in yellow) lay outside the catalytic site.

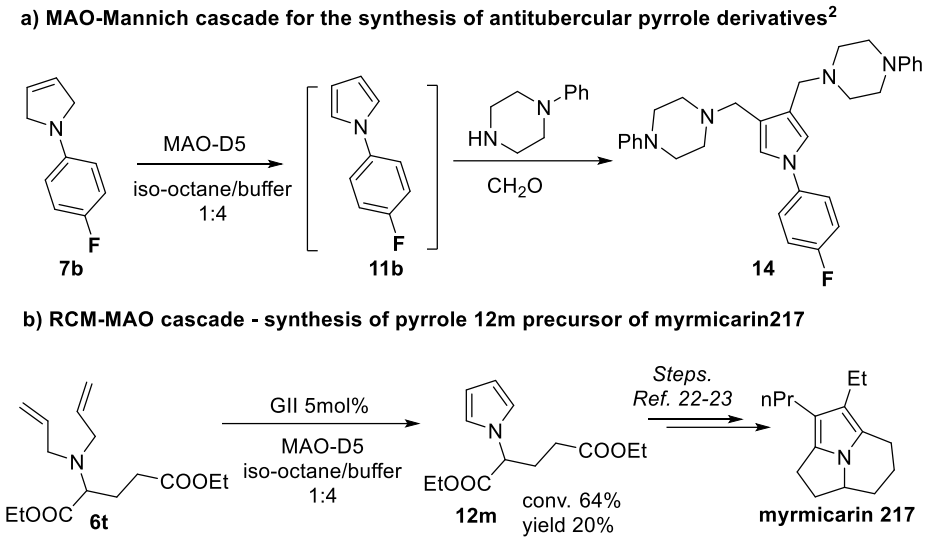
SCHEMES



Scheme 1. Synthesis of 3-pyrroline substrates **7** and **10**.



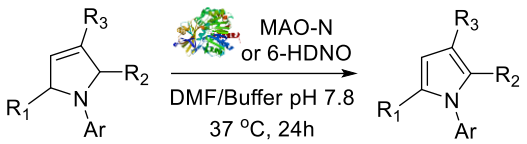
Scheme 2. Chemoenzymatic synthesis of pyrrole **12l**



Scheme 3. a) MAO-Mannich synthesis of pyrrole **14**. b) Synthesis of **12m**, precursor of myrmicarin217

TABLES.

Table 1. MAO-N and 6-HDNO aromatization of pyrrolines **7a-k**

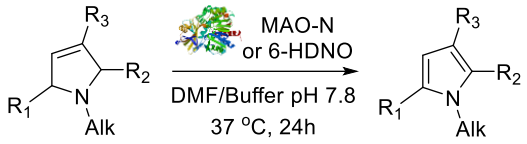


7a-k **11a-k**

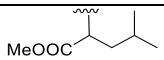
3-Pyr.	Ar	R_1	R_2	R_3	Biocat.[a]	Pyrrole	Conv (%)[b]
7a	Ph	H	H	H	MAO-D5	**11a**	61
					MAO-D9		32
					6-HDNO		60
7b	4-F-Ph	H	H	H	MAO-D5	**11b**	60
7c	4-Br-Ph	H	H	H	MAO-D5	**11c**	40
7d	4-iPr-Ph	H	H	H	MAO-D5	**11d**	>99
					MAO-D9		50
					6-HDNO		27
7e	4-MeO-Ph	H	H	H	MAO-D5	**11e**	82
					MAO-D9		54
					6-HDNO		21
7f	2,5-Me-Ph	H	H	H	MAO-D5	**11f**	45
					MAO-D9		34
					6-HDNO		30
7g	4-NO_2-Ph	H	H	H	MAO-D5	**11g**	2
7h	4-CN-Ph	H	H	H	MAO-D5	**11h**	2
7i	Ph	H	H	Me	MAO-D5	**11i**	>99
					MAO-D9		51
					6-HDNO		55
7j	Ph	Ph	H	H	MAO-D5	**11j**[c]	0
					MAO-D9		0
					6-HDNO		0
7k	Ph	H	H	Ph	MAO-D5	**11k**[c]	0
					MAO-D9		0

[a]Freeze-dried *E.coli* whole cells were used. [b]Conversion values were measured by GC-MS spectroscopy and/or ^{1}H-NMR. [c]Pyrrolines **7j-k** were also treated with MAO-D11 variant, but no conversion was observed.

Table 2. MAO-N and 6-HDNO catalysed aromatization of pyrrolines **10a-h** and **9**

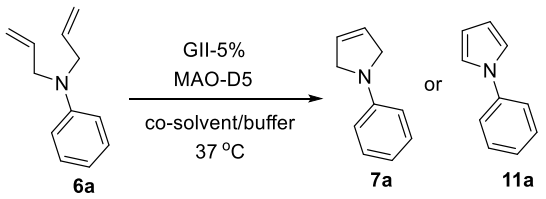


10a-k and 9 **12a-l**

3-Pyr.	Alk	R_1	R_2	R_3	Biocat.[a]	Pyrrole	Conv (%)[b]
10a	Bn	H	H	H	MAO-D5 MAO-D9 6-HDNO	**12a**	>99 61 95
10b	4-Cl-Bn	H	H	H	MAO-D5	**12b**	88
10c		H	H	H	MAO-D5	**12c**	>99
10d	Isovaleryl	H	H	H	MAO-D5	**12d**	>99
10e		H	H	H	MAO-D5	**12e**	>99
10f		H	H	H	MAO-D5 MAO-D9 6-HDNO	**12f**	>99 51 65
10g		H	H	H	MAO-D5	**12g**	56
10h		Me	Me	H	MAO-D5	**12h**	48
10i	4-Cl-Bn	Me	Me	H	MAO-D5	**12i**	51
10j	Me	H	H	Ph	MAO-D5 MAO-D9 6-HDNO	**12j**	92 78 87
10k	iPr	H	H	Ph	MAO-D5	**12k**	31
9c	H	H	H	Ph	MAO-D5 MAO-D9 6-HDNO	**12l**	33 57 10

[a]Freeze-dried *E.coli* whole cells were used. [b]Conversion values were measured by GC-MS spectroscopy and/or ^{1}H-NMR.

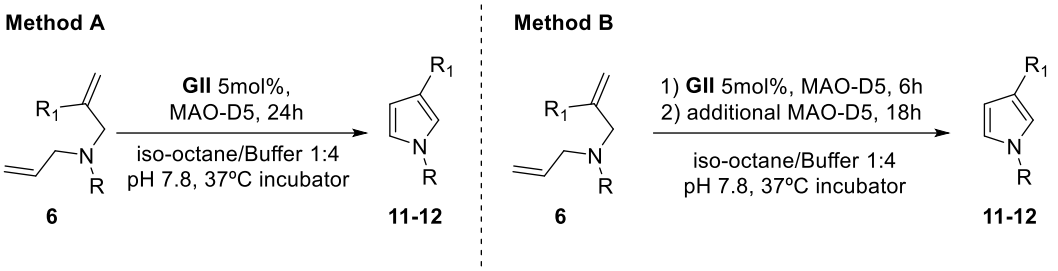
Table 3. Optimization of the chemoenzymatic cascade

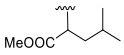


Entry	Co-Solvent	Buffer/Cosolvent	Ratio 6a/7a/11a (%)[a]
1	DMF	60:1	90/10/0
2	Acetone	60:1	10/90/0
3	-	100:0	5/95/0
4	DMSO	4:1	73/27/0
5	DCM	4:1	75/25/0
6	DMF	4:1	77/23/0
7	THF	4:1	92/8/0
8	Iso-octane	4:1	0/12/88

[a]Conversion values were measured both by GC-MS spectroscopy and/or ^{1}H-NMR.

Table 4. Chemoenzymatic cascade of diallyl anilines - substrate scope



Entry	Pyrrole	R	R_1	Conv. (%)[a]	Yield (%)[b]	Method
1	**11a**	Ph	H	88	78	A
2	**11a**	Ph	H	95	65	B
3	**11b**	4-F-Ph	H	86	63	A
4	**11b**	4-F-Ph	H	99	59	B
5	**11c**	4-Br-Ph	H	15	10	B
6	**11d**	4-iPr-Ph	H	35	22	A
7	**11d**	4-iPr-Ph	H	75	70	B
8	**11e**	4-MeO-Ph	H	50	42	B
9	**11f**	2,5-Me-Ph	H	25	20	A
10	**11i**	Ph	Me	87	45	B
11	**11l**	4-Cl-Ph	H	73	65	A
12	**11l**	4-Cl-Ph	H	90	56	B
13	**11m**	4-Me-Ph	H	99	50	A
14	**11m**	4-Me-Ph	H	90	45	B
15	**11n**	2-MeO-Ph	H	94	84	A
16	**11n**	2-MeO-Ph	H	81	72	B
17	**11o**	3,4-(OCH_2O)-Ph	H	84	57	B
18	**12a**	Bn	H	9	5	A & B
19	**12e**		H	63	41	B
20	**12g**		H	37	21	B
21	**12l**	H	Ph	0	0	B

[a]Conversion values were measured both by GC-MS spectroscopy as well as ^{1}H-NMR. [b]Isolated yields

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and full characterization for new compounds and intermediates are reported in the Supporting Information. Additional unsuccessful experiments are described. Copies of ^{1}H-NMR and ^{13}C-NMR spectra for new compounds are reported.

ACKNOWLEDGMENT

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REFERENCES

1. Bergman, J.; Janosik, T. In *Modern Heterocyclic Chemistry*; J. J. Alvarez- Builla, J. Vaquero,. J., Barluenga, Eds.; Wiley-VCH, Weinheim, 2011; Vol. 1.

2. a) Bhakta, S.; Scalacci, N.; Maitra, A.; Brown, A.K.; Dasugari, S.; Evangelopoulos, D.; McHugh, T.; Mortazavi, P. N.; Twist, A.; Petricci, E.; Manetti, F.; Castagnolo, D. *J. Med. Chem.***2016**, *59*, 2780–2793. b) Chachignon, H.; Scalacci, N.; Petricci, E.; Castagnolo, D. *J. Org. Chem.* **2015**, *80*, 5287-5295.

3. a) Cooney, J. V.; McEwen, W. E. *J. Org. Chem.***1981**, *46*, 2570–2573. b) Clauson-Kaas, N.; Tyle, Z. *Acta Chem. Scand.***1952**, *6*, 667.

4. Katritzky, A.; Jiang, J.; Steel, P. J. *J. Org. Chem.***1994**, *59*, 4551–4555.

5. Arcadi, A.; Rossi, E. *Tetrahedron*, **1998**, *54*,15253–15272.

6. a) Azizi, N.; Khajeh-Amiri, A.; Ghafuri, H.; Bolourtchian, M.; Saidi, M. R. *Synlett*, **2009**, 2245-2248. b) Rao, H. S. P.; Jothilingam, S.; Scheeren, H. W. *Tetrahedron*, **2004**, *60*, 1625-1630.

7. a) Donohoe, T. J.; Orr, A. J.; Gosby, K.; Bingham, M. *Eur. J. Org. Chem.***2005**, 1969–1971. b) Donohoe, T. J.; Kershaw, N. M.; Orr, A. J.; Wheelhouse, K. M. P.; Fishlock, L. P.; Lacy, A. R.; Bingham, M.; Procopiou, P. A.*Tetrahedron*, **2008**, *64*, 809-820.

8. De Matteis, V.; Dufay, O.; Waalboer, D. C. J.; van Delft, F. L.; Tiebes, J.; Rutjes, F. P. J. T., *Eur. J. Org. Chem.***2007**, 2667–2675.

9. a) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem. Int. Ed.***2003**, *42*, 4077-4082. b) Zhang, E.; Tian, H.; Xu, S.; Yu,X.; Xu, Q. *Org. Lett.***2013**, *15*, 2704-2707. c) Patil, R. D.; Adimurthy, S. *Adv. Synth. Catal.***2011**, *353*, 1695-1700.

10. Fagan, R. L.; Palfey, B. A. Comprehensive Natural Products II Chemistry and Biology **2010**, *7*, 37–113.

11. a) Ghislieri, D.; Green, A. P.; Pontini, M.; Willies, S. C.; Rowles, I.; Frank, A.; Grogan, G.; Turner, N. J. *J. Am. Chem. Soc.***2013**, *135*, 10863-10869. b) Ghislieri, D.; Houghton, D.; Green, A. P.; Willies, S. C.; Turner, N. J. *ACS Catal.***2013**, *3*, 2869–2872. c) Khöler, V.; Wilson, Y. M.; Durrenberger, M.; Ghislieri, D.; Churakova, E.; Quinto, T.; Knorr, L.; Haussinger, D.; Hollman, F.; Turner, N. J.; Ward, T. R. *Nature Chem.***2013**, 5, 93-99.

12. For a detailed description of the synthesis of 3-pyrroline precursors see Supp. Info.

13. Heath, R. S.; Pontini, M.; Bechi, B.; Turner, N. J. *ChemCatChem*, **2013**, *6*, 996-1002.

14. For further details on docking simulations and on the docking of pyrroline **10k** see the Supp. Info.

15. Gaweska, H.; Fitzpatrick, P. F. *Biomol. Concepts.* **2011**, *2*, 365–377.

16. a) Kim, J.-M.; Bogdan, M. A.; Mariano, P. S. *J. Am. Chem. Soc.***1993**, *115*, 10591–10595. b) Miller, J. R.; Edmondson, D. E. *Biochemistry*, **1999**, *38*, 13670–13683.

17. For further details on the mechanism of action of MAO see Supp. Info.

18. a) Denard, C. A.; Hartwig, J. F.; Zhao, H. *ACS Catal.* **2013**, *3*, 2856-2864. b) Wang, Y.; Zhao, H. *Catalysts* **2016**, *6*, 194. c) Palo-Nieto, C.; Afewerki, S.; Anderson, M.; Tai, C.-W.;

Berglund, P.; Córdova, A. *ACS Catal.* **2016**, *6*, 3932–3940. d) Díaz-Rodríguez, A.; Borzęcka, W.; Lavanderaand, I.; Gotor, V. *ACS Catal.* **2014**, *4*, 386–393. e) García-Junceda, E.; Lavandera, I.; Rother, D.; Schrittwieser, J. H. J. Mol. Catal. B-Enzym. **2015**, *114*, 1–6. f) Marcos, R.; Martin-Matute, B. *Isr. J. Chem.* **2012**, *52*, 639 – 652.

19. a) Tomasek, J.; Schatz, J. *Green Chem.***2013**, *15*, 2317-2338. b) Binder, J. B.; Blank, J. J.; Raines, R. T. *Org. Lett.***2007**, *9*, 4885–4888

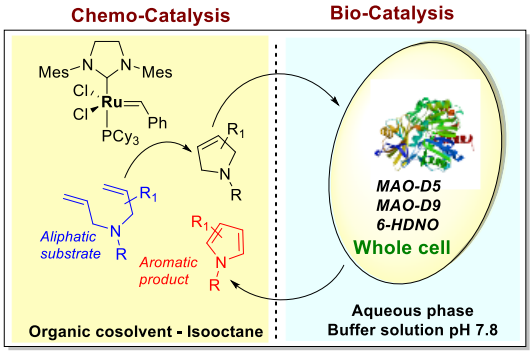
20. a) Denard, C. A.; Bartlett, M. J.; Wang, Y.; Lu, L.; Hartwig, J. F.; Zhao, H. *ACS Catal.***2015**, *5*, 3817–3822. b) Denard, C. A.; Huang, H.; Bartlett, M. J.; Lu, L.; Tan, Y.; Zhao, H.; Hartwig, J. F. *Angew. Chem. Int. Ed.***2014**, *53*, 465–469.

21. Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.***1992**, *114*, 7324–7325.

22. Jefford, C. W.; Sienkiewicz, K.; Thornton, S. R. *Helv. Chim. Acta* **1995**, *78*, 1511–1524

23. Ondrus, A. E.; Movassaghi, M. *Chem. Commun.* **2009**, 4151-4165.

SYNOPSIS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R
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Aromatic product
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MAO-D9
6-HDNO
Whole cell
Organic cosolvent - Isooctane
Aqueous phase
Buffer solution pH 7.8